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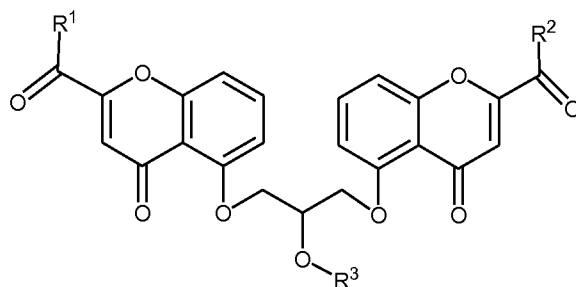
**REMARKS**

Claims 1-35 were presented at the time of filing. Claims 1, 2, 12, 13, 17, 22, 23 and 31-35 were canceled in applicants' response of April 28, 2010. Claims 3-11, 14-16, 18-21 and 24-30 are currently pending in the application, and the examiner has indicated that claims 3-11, 14-16, and 18-21 have been searched and examined. Claims 24-30 are currently withdrawn from consideration.

**Rejections under 35 USC §112**

Claims 3-11, 14-16 and 18-21 are rejected as being indefinite. The examiner alleges that the term "residues" of the parent groups does not indicate where the groups are attached. Applicants respectfully disagree.

The relevant portion of claim 3, from which the other claims depend, reads:

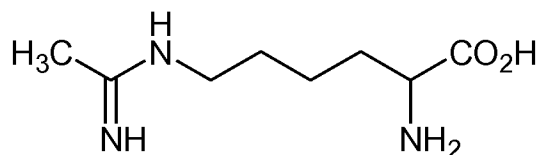
**I**

$R^3$  is chosen from hydrogen,  $-(C=O)R^4$ ,  $-(C=O)-G-O(C=O)R^4$ ,  $-(C=O)R^5$ ,  $-(C=O)NHR^6$  and  $-(C=O)OR^7$ ;

$-O(C=O)R^4$  is the deshydrogen residue of a carboxylic acid, the parent of which,  $R^4COOH$ , is an inhibitor of inducible nitric oxide synthase (iNOS);

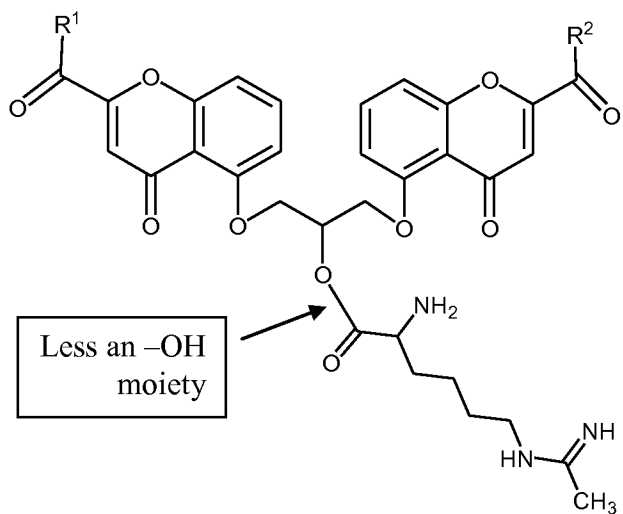
$-(C=O)R^4$  is the deshydroxy residue of a carboxylic acid, the parent of which,  $R^4COOH$ , is an inhibitor of iNOS;

If one were to choose B1 as the "parent"  $R^4COOH$

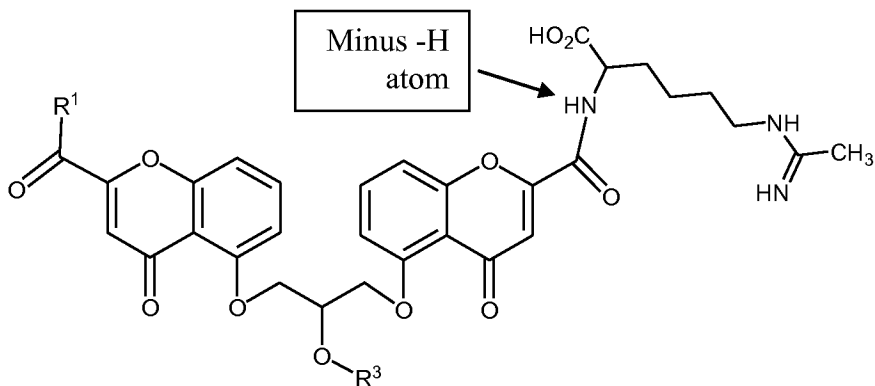
**B1,**

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it is clear that, when  $R^3$  is, for instance,  $-(C=O)R^4$ , then B1 is attached through the carboxylic acid end of the molecule, with the removal of a hydroxy moiety (deshydroxy residue). This results in the following formula:

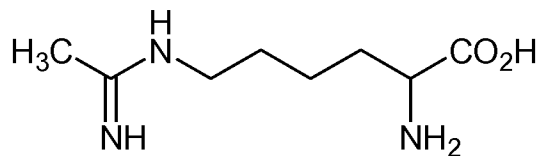


In a similar vein,  $R^2$  may be chosen to be  $-NHR^6$ , and  $-NHR^6$  is the deshydrogen residue of an amine, the parent of which is  $R^6NH_2$ . B1 could also be the parent compound in this case; however, the attachment would be at the amino group (less the hydrogen atom), rather than the carboxylic acid:



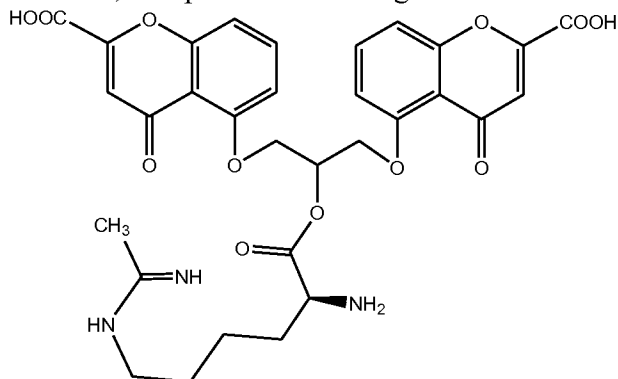
This explanation is contained in paragraph [0017] of the specification as well, reproduced below:

[0017] The concept of "parent", as used herein, refers to a compound, such as **B1**

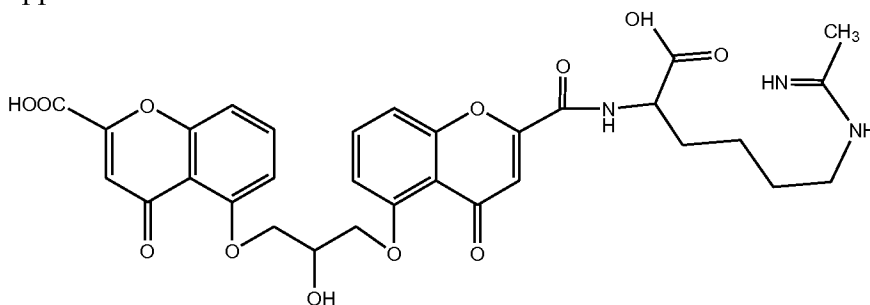
**B1**

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which is a selective inhibitor of iNOS. When the residue of this parent is attached to a chroman of formula I, one possible resulting structure is **512**:

**512**

in which  $R^3$  is  $-(C=O)R^4$  and  $-(C=O)R^4$  is the deshydroxy residue of a carboxylic acid, the parent of which, **B1**, is an inhibitor of iNOS. It will be immediately apparent that **B1** could also be attached to **I** as an amide:

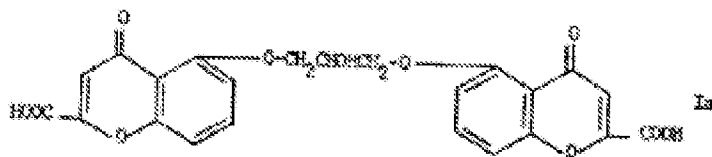
**508**

in which case  $R^2$  is  $-NHR^6$  and  $-NHR^6$  is the deshydrogen residue of an amine, the parent of which, **B1**, is an inhibitor of iNOS.

The text makes clear where the points of attachment are for a parent compound at various positions on the compound of Formula I. Based on this explanation, Applicants respectfully request the withdrawal of the 112 rejection.

### Rejections under 35 USC §102(b)

Claims 3-8, 10, 11 and 18 are rejected as anticipated by King, et al. (GB 1297264), and specifically formula Ia on page 3 of King:



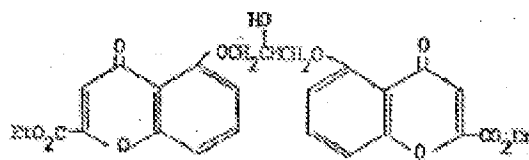
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The examiner states on page 3 of the Action that this compound anticipates the claims when “R<sup>3</sup> is H, and R<sup>1</sup> and R<sup>2</sup> are both OH.” However, claim 3 of the instant claims recites:

“...at least one of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> must be -G-O(C=O)R<sup>4</sup>, -NHR<sup>6</sup>, -OR<sup>7</sup>, -(C=O)R<sup>4</sup>, -(C=O)-G-O(C=O)R<sup>4</sup>, -(C=O)R<sup>5</sup>, -(C=O)NHR<sup>6</sup> or -(C=O)OR<sup>7</sup>....”

Since the claim precludes all of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> from being -OH, this claim is not anticipated by King.

Claims 3-8, 10, 11 and 18 are also rejected as anticipated by Wall, et al. (2,326,227), and specifically formula Ib on page 8:



In this case, both R<sup>1</sup> and R<sup>2</sup> are ethoxy groups, which, as above, is not an option allowed by claim 3. Therefore, the claims are not anticipated by Wall, and Applicants respectfully request the withdrawal of the 102(b) rejection for all cited claims.

### Rejections under 35 USC §103(a)

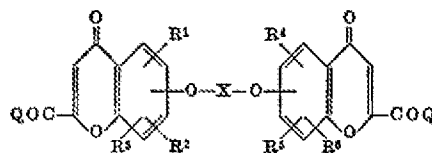
Claims 3-11, 14-16 and 18-21 are all rejected as obvious over King (GB 1297264), Johnson, et al. (3,790,580), WO9837079, US 6,355,689, US 5,863,931, Pizza, et al., and Vallance. Also tossed into the discussion, but not set forth in the initial presentation of the rejection, is Wall, German Offenlegungsschrift 2,326,227. The Examiner contends that the prior art references would point the person of skill toward the compounds of the instant invention. Applicants respectfully disagree. Applicants claim a bis(4-oxo-4H-chromene-2-carboxylic acid) having substituents R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>:

“...at least one of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> must be -G-O(C=O)R<sup>4</sup>, -NHR<sup>6</sup>, -OR<sup>7</sup>, -(C=O)R<sup>4</sup>, -(C=O)-G-O(C=O)R<sup>4</sup>, -(C=O)R<sup>5</sup>, -(C=O)NHR<sup>6</sup> or -(C=O)OR<sup>7</sup>...”.

None of the prior art references teaches or suggests these structures. The claims of the instant application are drawn to chemical structures, so the obviousness rejection should be based on chemical structures.

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The Examiner cites Johnson, et al. (US 3,790,580) as teaching anti-asthmatic compounds of formula



in which

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are the same or different and each represent hydrogen, halogen, hydroxy, alkyl or alkoxy, or substituted alkyl or alkoxy,  
 X is an optionally substituted, straight or branched hydrocarbon chain which may be interrupted by a carbocyclic or heterocyclic ring, or one or more oxygen atoms or carbonyl groups, and  
 COQ is a basic amide or a basic ester group.

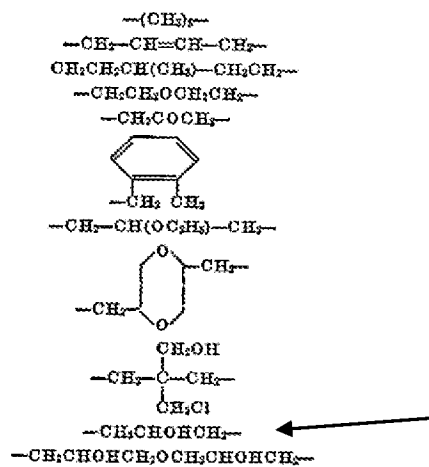
Johnson's broadest generic disclosure allows QOC- (corresponding to  $R^1$  and  $R^2$  of the instant claims) to be "a basic amide or a basic ester group" and gives specific examples of QOC- as:

Q is a group  $—ORNR'R''$  or a group  $—N(R^7)RNR^8R^9$ ,  
 R is a divalent alkylene group,  
 $R'$  and  $R''$ , which may be the same or different, are each hydrogen or alkyl, or  $R'$  and  $R''$ , together with the adjacent nitrogen atom form a 5 or 6 membered nitrogen heterocyclic ring,  
 $R^8$  and  $R^9$ , which may be the same or different, are each alkyl, or  $R^8$  and  $R^9$ , together with the adjacent nitrogen atom form a 5 or 6 membered nitrogen heterocyclic ring, and  
 $R^7$  is hydrogen, or alkyl.

None of these options overlaps with the options of the instant claims for  $R^1$  or  $R^2$ .

As regards applicants'  $R^3$ , Johnson allows X [which corresponds to  $—CH_2—CH(OR^3)—CH_2—$  of the instant application] to be "an optionally substituted, straight or branched hydrocarbon chain which may be interrupted by a carbocyclic or heterocyclic ring, or one or more oxygen atoms or carbonyl groups". Johnson lists specific X examples (in Column 3, lines 7-45) as various hydrocarbon chains which may be interrupted by oxygen atoms or carbonyl groups, by a ring, by halogen, by hydroxy or by alkoxy. Some specific examples are shown below:

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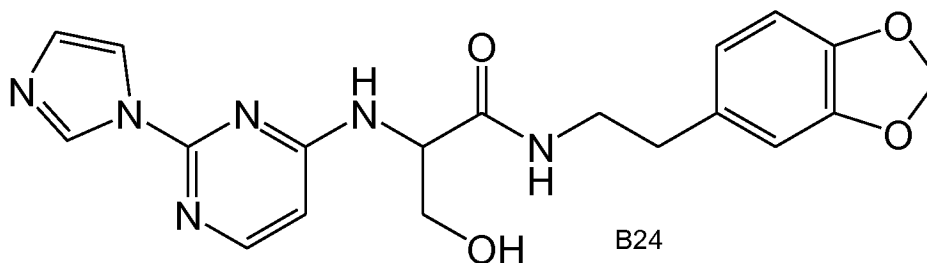


The configuration of X shown by the arrow above is the only option that would fall within the claims of the instant invention for  $R^3$ , and this would only be allowable when  $R^1$  and/or  $R^2$  of the instant claims fulfills the requirement of being chosen from  $-G-O(C=O)R^4$ ,  $-NHR^6$ , and  $-OR^7$ . Thus Johnson, by itself, discloses a chromenone core with certain esters and amides on the carboxylic acids, none of which corresponds to Applicants' esters and amides.

In formulating the obviousness rejection, the Examiner therefore adds King (GB 1297264), Wall, (OLS 326,227), Berlex (WO9837079), Beswick (US 6,355,689), Beams (US 5,863,931), Pizza, et al., and Vallance. Taking these seriatim:

1. King (GB 1297264): As discussed above under the 102 rejection, King discloses a compound in which  $R^1$  is OH,  $R^2$  is OH and  $R^3$  is hydrogen. The instant claims recite that "...at least one of  $R^1$ ,  $R^2$  and  $R^3$  must be  $-G-O(C=O)R^4$ ,  $-NHR^6$ ,  $-OR^7$ ,  $-(C=O)R^4$ ,  $-(C=O)-G-O(C=O)R^4$ ,  $-(C=O)R^5$ ,  $-(C=O)NHR^6$  or  $-(C=O)OR^7$ ...". King therefore adds nothing to the disclosure of Johnson. In fact, King provides even less. A person of skill would not be motivated to take the compound of King and alter it so greatly as to arrive at the compounds of the instant invention.
2. Wall, et al. (2,326,227) is also discussed above under the 102 rejection arguments, and is similar to King, in that  $R^1$  and  $R^2$  are each EtO- and  $R^3$  is hydrogen. Thus Wall also adds nothing to the disclosure of Johnson.
3. To provide a description of Applicants' substituents  $R^1$ ,  $R^2$  and/or  $R^3$ , the examiner adduces Example 53 of Berlex

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as well as unspecified disclosure in US 6,355,689 and US 5,863,931. Applicants are unable to find any evidence in these references that the compounds of each reference are meant to be used as anything other than stand-alone compounds. Further, nothing in these references remotely motivates the person of skill to believe that it would be advantageous to chemically modify the compounds disclosed in '079, '689 and '931 by replacing a hydrogen or hydroxyl with a 4-oxo-4H-chromene-2-carboxylic acid.

The Examiner further cites Pizza and Vallance to show that the inhibition of NOS with L-NAME or l-NMMA reduces inflammation and, on the basis of this, Pizza speculates that NOS inhibitors might be able to be used to treat asthma. However, this is all that these references disclose; there is no teaching of the specific compounds of the invention, nor, more importantly, is there any disclosure of the actual use of NOS inhibitors in the treatment of asthma.

What the examiner has created is a hodge-podge of references, assembled entirely by hindsight, each of which perhaps supplies an isolated element of applicants' claimed invention. (Although applicants question that the examiner has even established that NOS inhibitors treat asthma.) The mere statement that "The use of mast cell stabilizer with different substituents such an [sic] a basic amine or basic ester groups are know [sic] to treat asthma. One of skill in the art would be motivated to insert the other known NO inhibitor groups to make compounds that are inhibitors of NO and hence treat asthma." is not an "articulated reasoning" as required by MPEP 2141 III. Applicants respectfully request the withdrawal of this rejection.


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**Conclusion**

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

The Commissioner is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 08-1935, Reference No. 2221.008B.

Respectfully submitted,



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